Editorial

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Survival after sorafenib: Expect the unexpected

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In November 2007 sorafenib became the first systemic agent approved for the treatment of advanced hepatocellular carcinoma (HCC) [1]. Now, 6 years later we are still struggling to answer the [illegible] have shown, it is critical for us to understand how long patients live after they progress on sorafenib and what are the relevant prognosticators for outcome after sorafenib. While this information is relevant for the practicing clinician managing patients from day to day, it is especially important to have some benchmark for these data as we consider and design clinical studies for this population. In the past year we have seen the failure of 2 large randomized Phase III studies with promising new molecular agents in patients that have progressed on sorafenib [2,3]. Both brivanib and everolimus were moved into Phase III development based on uncontrolled Phase II data, which suggested activity based on our perceived understanding of how this population behaves after sorafenib failure [4–6]. Until recently, we have had to rely on assumptions from the Phase III sorafenib studies. In the SHARP study [1], time to progression (TTP) was 5.5 months in the treatment arm and median overall survival (OS) was 10.7 months suggesting that patients live about another 5 months after stopping sorafenib. Similarly, in the Asia-Pacific sorafenib Phase III study [7], TTP was 2.8 months and median OS was 6.5 months in the sorafenib arm accounting for about a median 3 months survival after stopping sorafenib. It is important to remember that in these studies the co-primary endpoints of overall survival and time-to symptomatic progression allowed patients to stay on sorafenib, even after they had RECIST defined radiologic progression as long as they were not symptomatic. In practice, given the opportunity to participate in clinical trials of new second-line agents, many clinicians will stop sorafenib when radiologic progression is documented, which may occur before the development of symptoms. This potentially is a source of lead time bias introduced into second line studies.

The current study by Shao and colleagues analyzed data from a single center in Taiwan on prognostic factors for survival in patients that progressed on first-line therapy [8]. The study included 192 patients treated on 6 different front-line protocols of systemic agents for advanced HCC. Of note, only a subset received sorafenib in the front-line setting either as a single agent [illegible] related liver disease. In this population, median OS following first-line therapy was only 4.0 months. The authors identified several factors associated with a better OS in their population, including Child-Pugh A, low CLIP score, and low ECOG performance status (PS). In addition, α-fetoprotein >400 ng/ml upon tumor progression and shorter TTP on front-line therapy were associated with a worse OS and having macrovascular invasion (MVI) upon progression had worse OS than having EHS alone. While many of these seem intuitive, and supported by observations made in cohorts of advanced HCC [9], they raise the possibility of including AFP, time on prior therapy, and separating MVI and EHS in stratification schemes. While having either MVI or EHS classify patients as BCLC stage C [9], in the sorafenib Phase III studies they were combined into one strata (i.e., the presence or absence of MVI/EHS). The recently completed BRISK-PS study evaluating brivanib in the second line setting suggests that these observations regarding AFP and MVI may be relevant in study design moving forward [2]. That is to say, perhaps they should be included as independent stratification factors as they seem to be prognostic. Ongoing data analysis of the control groups from the BRISK-PS study, as well as the everolimus study (EVOLVE-1) should be informative.

The authors also analyzed the subset of patients that would have qualified for one of 3 second-line clinical studies. These studies have focused on enrolling Child Pugh A patients with good PS, and adequate organ function. Of the 192 patients, about half, 94, would have qualified for one of the second line studies. Importantly, this subset had a different natural history than those that did not qualify. The median survival for those patients that qualified for the studies had a significantly longer OS than those that did not (Table 1). Again, while somewhat intuitive, these data start to inform us of the impact of patient selection "bias" in second-line clinical studies. Clearly, there is a subset of patients that do better after first-line progression than others. By enriching for these patients in Phase II uncontrolled signal finding studies, we may be over-interpreting significant activity from a new agent, when it is really the expected outcome for this group.

Another recent study evaluated post-progression survival in patients treated with sorafenib [10]. Unlike the current study,

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Table 1. Median overall survival for second-line patients depending on whether or not they met eligibility criteria for one of the studies listed above at progression on first-line therapy.

Study	OS eligible (mo)	OS ineligible (mo)
Brivanib phase II [4]	8.3	1.7
Brivanib phase III [2]	7.8	1.7
Tivantinib phase II	8.6	2.1

OS, median overall survival; mos, months.
Adapted from Shao et al [8].

this study was a prospective study following a cohort of 147 patients from the time they began sorafenib and evaluated TTP with pre-specified imaging assessments. In addition, this study was a single-center experience with a majority (57%) of patients with HCV related HCC. Median OS was 12.7 months from the start of the study. Several independent prognostic factors were identified in a multi-variate Cox analysis including baseline BCLC stage, PS, worsening liver function from CP A to CP B or C during treatment, and radiologic tumor progression. The authors also analyzed the pattern of progression and how that impacted overall survival and post-progression survival (PPS) and determined that survival was impacted in descending order from most to least favorable by intra-hepatic growth, extra-hepatic growth, new intra-hepatic lesion, new extra-hepatic lesion with OS of 16.8, 10.7, 15.6, and 12.2 months, respectively. Similar to the study by Shao *et al.* this study also identified BCLC stage, PS, and CP status at the time of progression as predictors of post-progression survival (PPS) in addition to progression defined by a new extra-hepatic lesion. For patients that would qualify for a second line study, the PPS was significantly longer than the general population with median OS of 13.6 months and this is effected by the pattern of progression observed in first-line; a potential important new prognostic factor to include in new studies of this population. Like the current study in this month's *Journal*, it is clear that the population of patients that are meeting the common inclusion criteria for second-line studies have a more favorable natural history than the general HCC population.

Since sorafenib's approval there have been at least 5 Phase III failures in front- and second-line HCC. To avoid this in the future, it is critical that we change our approach to the development of systemic therapies. For one, randomized Phase II studies must be done to establish efficacy. The lack of reliable surrogate endpoints for survival such as response, TTP, or PFS to correlate with OS in this disease and, as highlighted in this manuscript, the clinical heterogeneity of the disease make it impossible to know if a new agent is really active unless it is compared to a control group. In front-line this would be sorafenib and in second-line this would be placebo. In addition, spending more time on the development of predictive markers of response both pre-clinically and in early clinical development would help enrich for patients most likely to benefit. It is quite likely that active drugs have failed, or been interpreted as inactive because the responding population was not well-represented in the study. The development of tivantinib, a small molecule inhibitor of the MET receptor can serve as a paradigm. A randomized phase II study was performed with correlative biomarker work showing that high Met-expression may identify a group of patients that benefit most from the drug [11]. While this is hypothesis generating, it is now a strategy for patient selection being employed in a prospective Phase III study.

In summary, the development of systemic therapy in HCC is still evolving. We are learning that our current expectations of the natural history are not as we expected. In order to move the field forward, it is critical that we learn from negative studies, and integrate the lessons learned into future studies; otherwise we are likely to continue to see negative trials in HCC. As Albert Einstein once said, "Insanity is doing the same thing over and over again and expecting different results".

Conflict of interest

The author declared a relationship with Bayer, Onyx, Novartis and Bristol Myers Squibb.

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